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13. ABSTRACT *(Maximum 200 words)*

The performed research demonstrates that important ligand classes can be synthesized on solid supports and can be used directly without purification to prepare asymmetric catalysts. For the catalyst system that was evaluated, the ligands prepared in parallel on support provided comparable enantioselectivities to purified ligands prepared individually over several steps in solution. Enantioselectivities greater than 90% ee were observed. These results hold promise for parallel synthesis and evaluation approaches in asymmetric catalyst optimization.

A sulfinamide chiral auxiliary has also been developed. Auxiliary loading, diastereoselective transformations, and auxiliary removal all proceed in high yields. Auxiliary removal is accomplished by first activating the auxiliary linkage followed by nucleophilic release. Modification of the sulfinamide auxiliary as a support-bound linkage will allow the stereodefined synthesis of libraries of chiral compounds.

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FINAL REPORT

Grant#: N00014-94-1-0628

PRINCIPLE INVESTIGATOR: Jonathan A. Ellman

INSTITUTION: University of California at Berkeley

GRANT TITLE: Combinatorial Strategies Applied to Catalyst Development

AWARD PERIOD: 1 June 1994 - 31 May 1997

OBJECTIVE: The funded research had two objectives. (1) To apply simultaneous synthesis and then simultaneous screening strategies to develop metal-based catalysts. (2) To develop a support-bound "safety-catch" chiral auxiliary. This solid support linker would be of considerable utility for the stereodefined synthesis of libraries of chiral compounds. Kenner has defined a safety-catch linker as a support linkage that is stable under most reaction conditions but that can be activated under a specific set of conditions, in analogy to releasing the safety on a gun, to allow the nucleophilic release of the final product from the solid support.

APPROACH: Objective (1): Multiple ligands are prepared simultaneously, in parallel on solid support. Appropriate metals are then introduced, and the resulting metal complexes are evaluated for their ability to catalyze different reactions. Objective (2): The safety-catch chiral auxiliary for solid-phase synthesis is loosely based upon previous safety-catch linkers that were developed in our group and that are currently sold by three different resin supply companies (see Backes, B. J.; Virgilio, A. A.; and Ellman, J. A. *Am. Chem. Soc.*, **1996**, *114*, 3055-3057 and references therein). Chiral auxiliary evaluation is first being performed in solution where modifications of the auxiliary can be introduced most rapidly. The next step is to develop the support-bound variant.

ACCOMPLISHMENTS:

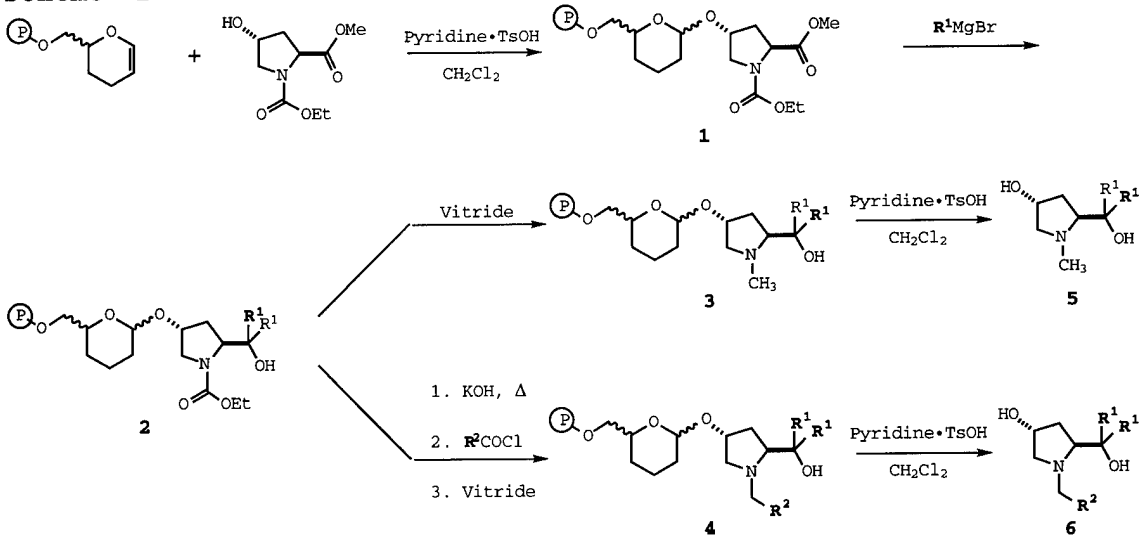
OBJECTIVE (1)
Towards objective (1) we have accomplished two goals. (1) We have developed general and high yielding solid-phase synthesis methods to construct pyrrolidinylmethanol ligands. Members of this ligand class are employed extensively in asymmetric dialkylzinc additions to aldehydes and in the asymmetric reduction of ketones. In addition, ligands of related structures have been employed in asymmetric aldol and Diels Alder reactions. (2) We have demonstrated that a range of ligands of this class prepared by the above solid-phase methods can be evaluated directly in asymmetric transformations without purification. These two results demonstrate that library synthesis and evaluation is feasible.

The pyrrolidinylmethanol ligand synthesis sequence is outlined in Scheme 1. The ethyl carbamate of 4-hydroxyproline methyl ester is coupled to a

solid-support using a tetrahydropyranyl linker to provide support-bound derivative **1**. Excess Grignard reagent is then added to provide support-bound tertiary alcohol **2**. A number of different Grignard reagents add in high yield including both aliphatic and aromatic Grignard reagents. Direct reduction of alcohol **2** provides N-methyl ligand **3**. Alternatively, the ethyl carbamate can be removed by treatment of **2** with potassium hydroxide in 2:1 dioxane/butanol. Subsequent acylation with an acid chloride followed by reduction with Vitride then provides the support-bound ligand **4**.

The support-bound ligands can be evaluated directly in asymmetric transformations, or they can be cleaved from the support with pyridinium *p*-toluenesulfonate followed by evaluation of free ligands, **5** or **6**, in solution. In practice we have found that catalyst evaluation is most reliable when the ligands are first removed from the solid-support due to a deleterious support effect that we have at this point not been able to overcome. A number of ligands have been prepared in this fashion and have been evaluated in asymmetric dialkylzinc additions to both benzaldehyde and isovaleraldehyde. Enantioselectivities greater than 90%ee were observed for some of the prepared ligands. The unpurified ligands that were prepared on solid-support provide the same addition enantioselectivity that is provided by purified ligands. In addition, the auxiliary 4-hydroxyl group does not appear to have any effect upon the level of asymmetric induction.

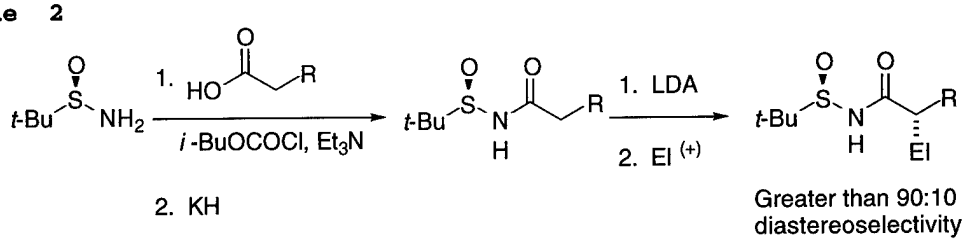
Scheme 1



OBJECTIVE (2)

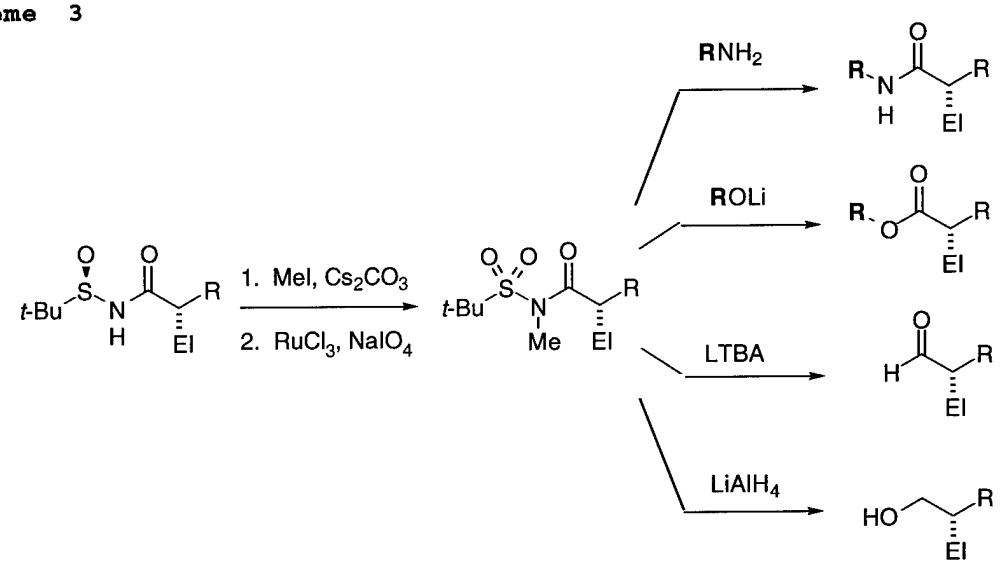
We previously demonstrated that chiral *t*-butylsulfinamides serve as efficient chiral auxiliaries for diastereoselective enolate alkylation reactions (see Scheme 2).

Scheme 2



We have further demonstrated that the alkylation products can be cleanly activated by *N*-alkylation and oxidation. Addition of a variety of nucleophiles then provides access to diverse products as is shown in Scheme 3. All of the transformations proceed in high overall yields.

Scheme 3



CONCLUSIONS:

OBJECTIVE (1):
The performed research demonstrates that important ligand classes can be synthesized on solid supports and can be used directly without purification to prepare asymmetric catalysts. For the catalyst system that was evaluated, the ligands prepared in parallel on support provided comparable enantioselectivies to purified ligands prepared individually over several steps in solution. These results hold promise for parallel synthesis and evaluation approaches in asymmetric catalyst optimization.

OBJECTIVE (2):
A sulfinamide chiral auxiliary has been developed in solution. Auxiliary loading, diastereoselective transformations, and auxiliary removal all proceed in high yields. Auxiliary removal is accomplished by first activating the auxiliary linkage followed by nucleophilic release. Modification of the sulfinamide auxiliary as a support-bound linkage will allow the stereodefined synthesis of libraries of chiral compounds.

SIGNIFICANCE:

OBJECTIVE (1):
Even though considerable design is employed in the development of chiral ligands and in the choice of metals for the development of catalysts for asymmetric transformations, catalyst optimization still generally requires the evaluation of numerous ligands and metals, as well as reaction conditions. For many asymmetric transformations, the catalyst and/or reaction conditions must be optimized for each substrate or reagent class thereby greatly increasing the number of experiments that must be performed. We have demonstrated that the simultaneous synthesis of the pyrrolidinylmethanol ligand class can be performed on solid-support, and that the resulting ligands are of sufficient purity for reliable evaluation as catalysts without purification. These results demonstrate that combinatorial strategies can be applied to greatly expedite the development of asymmetric catalysts.

Objective (2):
The synthesis and evaluation of compound libraries to identify a useful compound structure for a particular application is increasingly being used for the development of new drugs, catalysts, and materials. While general methods to prepare libraries displaying diverse functionality are available, better methods to control the spatial display, or stereochemistry, of functionality is needed. Chirality can often be as important as the type of functionality that is displayed in determining the properties of a compound. A support-bound, safety-catch chiral auxiliary will greatly expedite the synthesis of libraries of chiral compounds. The support-bound auxiliary should not only provide good diastereofacial selectivity, but also a robust support linkage to allow as wide an array of chemistry to be performed as possible. A method for activation of the support linkage for nucleophilic release of the compound into solution should then be possible at the end of the solid-phase synthesis sequence. This process provides access to pure products with a final element of diversity being introduced in the release step.

PATENT INFORMATION: None

AWARDS: Joel H. Hildebrand Chair in Chemistry (for Associate Prof.)
Alfred P. Sloan Fellowship

PUBLICATIONS:

(1) Liu, G.; Ellman, J. A. "Combinatorial Asymmetric Catalyst Development. General Solid-Phase Synthesis Strategy for the Preparation of 2-Pyrrolidinemethanol Ligands" *J. Org. Chem.* **60**, 7712-7713 (1995).

(2) Backes, B. J. and Ellman, J. A. "*t*-Butylsulfinamide as a Safety-Catch Chiral Auxiliary for Enolate Alkylations", manuscript in preparation.